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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

GAMETT, DANIEL C

ART UNIT

PAPER NUMBER

1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/581,856	Applicant(s) TUR ET AL.	
	Examiner DANIEL C. GAMETT	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20-23, 26-28, 33-36, 53, 54, 58-62, 69 and 72-85 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-23, 26-28, 33-36, 53, 54, 58-62, 69, and 72-85 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendments of 03/05/2010 have been entered in full. Claims 1-19, 24, 25, 29-32, 37-52, 55-57, 63-68, 70 and 71 are cancelled. Claims 20-23, 26-28, 33-36, 53, 54, 58-62, 69, and 72-85 are under examination.
2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn in view of Applicants' amendment and/or arguments filed 03/05/2010.

Claim Objections

3. Claims 23, 73, 74, and 79-81 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A cytokine that is mutated at one or more of positions 191, 267, and 269 (claim 23) would not be a cytokine that "has the amino acid sequence of SEQ ID NO: 1, except that it is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220", as in claim 20. Claim 20 literally only allows the recited exceptions to SEQ ID NO: 1. Claims 73, 74, and 79-81 likewise recite mutations outside of the scope of claims 20-22, from which they depend.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 35, 36, 75, 76, 82, and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 35 and 36 recite a “TRAIL cytokine *having* the amino acid sequence of SEQ ID NO: 1 with selectivity for a target receptor, wherein the TRAIL cytokine sequence *has been altered* ...” This recitation does not have the same meaning as “wherein said cytokine has the amino acid sequence of SEQ ID NO: 1, except that it is mutated at one or more amino acid positions” as in claim 15, for example. Furthermore, this recitation does not define a sequence of starting material for a process of mutagenesis and selection, as in claim 53, for example. The added emphasis shows that this recitation in claims 35 and 36 is self-contradictory, as it defines a product that both has and does not have the amino acid sequence of SEQ ID NO: 1.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20-23, 26-28, 33-36, 53, 54, 58-62, 69, and 72-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The

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claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. The independent claims have been amended to recite a cytokine that is “mutated at one or more of the positions 130, 131, 149, 160, 195, 214, 218, 220 to an amino acid other than alanine”. **This is a new matter rejection**, insofar as it is found that the specification as filed does not support the concept of a genus of mutations to “an amino acid other than alanine”. Alternatively, it is found that even if the specification is interpreted to support the *concept* of the genus of mutations to “an amino acid other than alanine”, the specification does not provide adequate description of the genus as broadly claimed.

9. Applicants assert that support for the claim amendments is found in the claims as originally filed and on pages 5 and 55-56 of the specification. The original claims did indeed recite mutations at the recited positions and, where an amino acid was recited, the mutants did not substitute alanine for the wild-type amino acid. The original claims, however, did not recite the genus of mutations to “an amino acid other than alanine”. Pages 55-56 of the specification provide the reference amino acid and coding nucleotide sequences for the TRAIL cytokine. These do not teach any specific mutations or the genus of mutations to “an amino acid other than alanine”. Therefore, support for the claimed genus must rely on page 5 of the specification. The specification teaches on page 5, lines 9-18, that a potential disadvantage of the prior art method of constructing a library using positions derived from an alanine scan, is that other advantageous mutations for achieving receptor selectivity/specificity at positions not found in the alanine scan library are missed. “Positions e.g. 195 and 218 were screened in the alanine scan, however

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mutation to alanine did not yield a clear indication for shifting selectivity and therefore those positions were not included in the library.”

10. Therefore, the concept of a genus of mutations to “an amino acid other than alanine” is not literally supported. Support for this concept relies upon inference based on the assertion that alanine scanning mutagenesis of TRAIL has been done in the past, and two recited positions, 195 and 218, “did not yield a clear indication for shifting selectivity.” These prior alanine scanning results, together with the disclosure that the currently recited mutations do alter selectivity, *might* be taken to infer support for a genus wherein positions 195 and 218 are mutated to an amino acid other than alanine (It will be argued below that even this is not supported). The specification makes no specific assertion of prior negative results for alanine mutants for the other recited positions. It appears therefore, that the specification does not contemplate a genus of mutations to an amino acid other than alanine, but instead aims only to make the point that potentially important mutations may be missed by alanine-scanning mutagenesis.

11. Furthermore, the inference would hold only IF it is accepted that alanine substitutions at positions 195 and 218 do not in fact “yield a clear indication for shifting selectivity”. In this regard, it is important to consider the selectivity contemplated in the claims. The claims recite “an increase in binding affinity and selectivity/specificity of the cytokine protein for that target receptor”. Thus, the claims generically recite any TRAIL receptor, not just the DR4, DR5, DcR1 or DcR2 tested in the instant disclosure. US 6740739 (of record) shows that the D218A mutation confers tighter affinity for OPG, but not DR4, DR5, or dcR2 (Example 19, FIG. 19). This directly contradicts any idea that position 218 must be mutated to an amino acid other than alanine in order to increase in binding affinity and selectivity/specificity of TRAIL for any or all

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of its target receptors, as recited by the claims. Therefore, even if the specification were deemed to contemplate a genus wherein positions 195 and 218 must be mutated to an amino acid other than alanine, this genus could not include any embodiments where such mutation is required for the changes in binding affinity and selectivity/specificity recited in the instant claims.

12. Therefore, the amendments of 03/05/2010 introduce new matter which is not supported by the specification as filed.

Conclusion

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646